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10/772,037	02/04/2004	Patrick W. Gray	27866/39986	4170

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/772,037	GRAY ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Claims 51-57 are pending and under examination.

Benefit to an Earlier Filed US Application

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Applicant claims benefit to US Application 08/575,967 (12/20/1995), now US Patent 6,265,184; US Application 08/661,393 (06/17/1996) now US Patent 6,268,477; and US Application 08/771,276 (12/20/1996), now US Patent 6,797,811. However, the specification in 08/575,967, now US Patent 6,265,184, fails to disclose the instant method of modulating a chemokine receptor or method of inhibiting HIV/SIV infection of cells. Benefit is granted to 06/17/1996, as the instant method is disclosed in 08/661,393, now US Patent 6,268,477 and 08/771,276 now US Patent 6,797,811.

Objections to the Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method of modulating CCR5.

4. The disclosure is objected to because of the following informalities:

a. The word "and" is inappropriately capitalized on p. 12, line 7.

Appropriate correction is required.

Objections to the Abstract

5. The abstract of the disclosure is objected to because the instant invention is not drawn to polynucleotides or assays utilizing polynucleotides. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire

disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

(1) if a machine or apparatus, its organization and operation;

(2) if an article, its method of making;

(3) if a chemical compound, its identity and use;

(4) if a mixture, its ingredients;

(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 51-53 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing infection of simian CD4+ Tcells using an anti-CD88C antibody, does not reasonably provide enablement for modulating HIV or SIV infection in mammalian subjects, or modulating HIV infection of cells, including HEK, HeLa, U373 cells, cat CCC cells, and HeLa-MAGI cells by administering a composition comprising the recited antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence

of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a method for modulating chemokine receptor 88C-mediated HIV or SIV infection of cells comprising the step of administering to a mammalian subject a composition comprising an antibody selected from the recited group, wherein the mammalian subject is infected with HIV or SIV and wherein the antibody is administered in an amount effective to modulate HIV or SIV infection of 88-C expressing cells in said subject; wherein said antibody is a humanized antibody; a method of modulating chemokine receptor 88C-mediated HIV or SIV infection of cells comprising the step of administering to a mammalian subject a composition comprising a polypeptide comprising an antigen-binding fragment of an antibody selected from the recited group, wherein the mammalian subject is infected with HIV or SIV and wherein the antibody is administered in an amount effective to modulate HIV or SIV infection of 88C-expressing cells in said subject; where in the composition further comprises a pharmaceutically acceptable carrier.

The nature of the invention is drawn to a method for modulating the chemokine receptor 88C (also known as the RANTES receptor or CCR5) -mediated HIV or SIV infection by administering a composition comprising an antibody that blocks the CCR5 chemokine receptor, which is a co-receptor for HIV and SIV in primates.

The state of the art teaches that lentiviruses, including HIV and SIV, are species-specific, exogenously transmitted retroviruses that have a unique ability to replicate continuously but at a restricted rate in host tissues. This property is thought to be related to the retroviral nature of the replication process (RNA to DNA to RNA) and to the ability of the viruses to do this in cells of the macrophage lineage (see, Narayan. Can J Vet Res. 1990 Jan;54(1):42-8, abstract).

The state of the art also discloses that there are two classes of 88C/CCR5 antagonists in commercial development— a monoclonal antibody to CCR5 and several small molecule antagonists (see i.e., Lederman et al., JAMA 2006 Aug 16;296(7):815-26, especially at 823, columns 1 and 2). "The humanized monoclonal antibody HGS Ab004 (Human Genome Sciences, Rockville, Md) binds to the second extracellular loop of CCR5, thereby inhibiting both chemokine and HIV envelope binding. Small molecule CCR5 inhibitors aplaviroc (GlaxoSmithKline. Philadelphia, Pa), maraviroc (Pfizer, New York, NY), and vicriviroc (Schering-Plough, Kenilworth, NJ) have been tested for activity in large-scale human trials. Each of these small molecules is likely to be an allosteric inhibitor that locks CCR5 into a conformation such that it is not able to bind HIV envelope protein. Each can function as a receptor

antagonist, blocking to various degrees the signals induced by different receptor-binding chemokines. None of these agents is thought to promote signaling and receptor internalization, therefore, these agents are not likely to promote inflammation as agonists might." Lederman et al., also disclose that "[t]hrough interactions with its chemokine ligands, the chemokine receptor CCR5 helps to initiate immune responses and to distribute effector immune cells to sites of inflammation. CCR5 is also a key cellular receptor that is required for almost all instances of HIV infection. Strategies targeting CCR5 are therefore in development for prevention and treatment of HIV infection. Although deletion of CCR5 is generally well tolerated in mice and in humans, with sufficient challenge, a perturbed host immune response can be demonstrated in both. Whether pharmacological inhibition of CCR5 function will be as well tolerated or whether blocking this receptor will have special adverse consequences in persons with underlying HIV-related immune impairment remains to be seen " (Lederman et al., JAMA 2006 Aug 16;296(7):815-26, at 824, column 1, last paragraph to column 2).

The level of skill of those in the art is extremely high due to the complex nature and species specificity of viral immunology. Nine examples are provided in the instant disclosure. However, only three are somewhat relevant to the instant claims. Examples 6 and 7 are directed to the role of 88C/CCR5 as a co-receptor for HIV and example 8 is directed to the preparation and characterization of monoclonal and polyclonal antibodies that are immunoreactive with 88C/CCR5. Even so, the only example of using an anti-88C antibody to decrease and/or "modulate" lentiviral infection is found on p. 39 of the specification, lines 14-24, which discloses five anti-88C monoclonal antibodies were tested for their ability to block infection of cells by SIV. Simian CD4+ Tcells were incubated with SIVmac32HJ5 clones in the presence of the anti-88C antibody. SIV infection was measured by determining reverse transcriptase activity after 9 days. Four of the antibodies were able to block SIV infection. Antibody 227K blocked infection by 53%, antibody 227M by 59%, antibody 227N by 47% and 227P by 81%. Antibody 227R did not block SIV infection. No data are given on decreasing and/or modulating HIV infection of any cell or subject from any mammalian species.

Applicants' claims are excessively broad due, in part, to the lack of guidance in the disclosure about whether the claimed antibodies are capable of "modulating" infection of cells or subjects by HIV. Applicant discloses use of HEK, HeLa, U373, HeLa-MAGI, and cat CCC cells infected with HIV and/or SIV. However, Applicant has failed to provide any guidance, teaching, or data to show whether any anti-88C (anti-CCR5) antibodies were able to prevent HIV infection of any of these cell lines. Applicant discloses data regarding the ability of HIV to infect these cell lines, but fails to teach the modulation of this infection by the claimed method. Further, because lentiviruses are known to be species-specific in

their infectivity, applicants have not shown that the claimed method is applicable to the broad genus of mammalian species claimed (see, i.e. Narayan. Can J Vet Res. 1990 Jan;54(1):42-8, abstract).

Therefore, based on the discussions above concerning the art's recognition that lentiviruses are known to be species-specific and the use of anti-88C/CCR5 antibodies is unclear in terms of decreasing and/or preventing infection by HIV, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine whether the recited anti-88C/CCR5 antibodies modulate the infection of cells and/or mammalian subjects by HIV and/or SIV.

Due to the large quantity of experimentation necessary to determine whether infection by HIV and/or SIV in cells and mammalian subjects may be modulated by the recited anti-88C/CCR5 antibodies, such that it can be determined how to use the claimed methods, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that lentiviruses are known to be species-specific and the use of anti-88C/CCR5 antibodies is unclear in terms of decreasing and/or preventing infection by HIV, and the breadth of the claims which fail to recite particular mammalian species, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 54-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of inhibiting infection of simian CD4+ Tcells using an anti-CD88C antibody, does not reasonably provide enablement for inhibiting HIV infection in mammalian cells or subjects, or inhibiting SIV infection of non-simian cells by administering a composition comprising the recited antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a method for inhibiting human or simian immunodeficiency virus (HIV or SIV) infection of cells, comprising the step of contacting cells at risk for infection with HIV or SIV with an

antibody selected from the recited group, wherein the antibody is administered in an amount effective to inhibit HIV or SIV infection of 88C-expressing cells in said subject.

The state of the art teaches that lentiviruses, including HIV and SIV, are species-specific, exogenously transmitted retroviruses that have a unique ability to replicate continuously but at a restricted rate in host tissues. This property is thought to be related to the retroviral nature of the replication process (RNA to DNA to RNA) and to the ability of the viruses to do this in cells of the macrophage lineage (see, Narayan. Can J Vet Res. 1990 Jan;54(1):42-8, abstract). The state of the art also discloses that "[a]lthough deletion of CCR5 is generally well tolerated in mice and in humans, with sufficient challenge, a perturbed host immune response can be demonstrated in both. Whether pharmacological inhibition of CCR5 function will be as well tolerated or whether blocking this receptor will have special adverse consequences in persons with underlying HIV-related immune impairment remains to be seen " (Lederman et al., JAMA 2006 Aug 16;296(7):815-26, at 824, column 1, last paragraph to column 2).

The level of skill of those in the art is extremely high due to the complex nature and species specificity of viral immunology. Nine examples are provided in the instant disclosure. However, only three are somewhat relevant to the instant claims. Examples 6 and 7 are directed to the role of 88C/CCR5 as a co-receptor for HIV and example 8 is directed to the preparation and characterization of monoclonal and polyclonal antibodies that are immunoreactive with 88C/CCR5. Even so, the only example of using an anti-88C antibody to decrease and/or "modulate" lentiviral infection is found on p. 39 of the specification, lines 14-24, which discloses five anti-88C monoclonal antibodies were tested for their ability to block infection of cells by SIV. Simian CD4+ Tcells were incubated with SIVmac32HJ5 clones in the presence of the anti-88C antibody. SIV infection was measured by determining reverse transcriptase activity after 9 days. Four of the antibodies were able to block SIV infection. Antibody 227K blocked infection by 53%, antibody 227M by 59%, antibody 227N by 47% and 227P by 81%. Antibody 227R did not block SIV infection. No data are provided on inhibiting HIV infection of any cell or subject from any mammalian species.

Applicants' claims are excessively broad due, in part, to the lack of guidance in the disclosure about whether the claimed antibodies are capable of inhibiting infection of cells or subjects by HIV. Applicant discloses use of HEK, HeLa, U373, HeLa-MAGI, and cat CCC cells infected with HIV and/or SIV. However, Applicant has failed to provide any guidance, teaching, or data to show whether any anti-88C (anti-CCR5) antibodies were able to prevent HIV infection of any of these cell lines. Applicant fails to show any data or provide any guidance regarding inhibition of HIV or SIV infection in a subject. Further, because lentiviruses are known to be species-specific in their infection, applicants have not

shown that the claimed method is applicable to the broad genus of subjects claimed (see, i.e. Narayan. Can J Vet Res. 1990 Jan;54(1):42-8, abstract). Moreover, applicants have not adequately provided guidance on what is meant by the "inhibition" of infection. There is nothing in the disclosure to convey the degree to which the inhibition is to occur or whether any level of inhibition is contemplated to be sufficient.

Therefore, based on the discussions above concerning the art's recognition that lentiviruses are known to be species-specific and the use of anti-88C/CCR5 antibodies is unclear in terms of inhibiting infection by HIV, the specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine whether the recited anti-88C/CCR5 antibodies inhibit the infection of cells and/or mammalian subjects by HIV and/or SIV.

Due to the large quantity of experimentation necessary to determine whether infection by HIV and/or SIV in cells and subjects may be inhibited by the recited anti-88C/CCR5 antibodies, such that it can be determined how to use the claimed methods, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that lentiviruses are known to be species-specific and the use of anti-88C/CCR5 antibodies is unclear in terms of inhibiting infection by HIV, and the breadth of the claims which fail to recite particular subjects, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Enablement

9. Claims 51-57 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Elements that are critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification does not reasonably provide enablement for inhibition (prevention/prophylaxis) of HIV or SIV infection in any species by any means. The skilled artisan cannot envision the prevention/prophylaxis of HIV or SIV infection. Prevention/prophylaxis involves "attacking" the underlying cause of HIV or SIV; i.e., completely disrupting the viral infection mechanisms which give rise to HIV or SIV. The skilled artisan is aware that the etiology of different trophic species of HIV and SIV weren't entirely known at the time of the invention herein. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention.

In this case, the specification must disclose a means of preventing HIV or SIV regardless of the underlying causes of the infection, which could include 88C/CCR5 involvement. The teachings of the specification do not enable a person of ordinary kill in the art to make and use the claimed method of prevention/prophylaxis. Moreover, "[p]atent protection is granted only in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Genentech Inc. v. Novo Nordisk A/S, 108 F.3d at 1366, 42 USPQ2d at 1005 (Fed. Cir.), cert. denied, 118 S. Ct. 397 (1997), ("Tossing out the mere germ of an idea does not constitute an enabling disclosure").

Claim Rejections - 35 USC § 112, Second Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 54-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method for inhibiting HIV or SIV infection of cells. It is unclear from the claims, as written, whether the method is drawn to inhibiting HIV or SIV infection of cells *in vivo*, *in vitro*, or *in situ*. The preamble of claims 54 and 56 appear to recite an *in vitro* or *in situ* method, while the wherein clauses appear to recite an *in vivo* method.

12. Claims 54-56 recite the limitation "said subject" in the last line of claims 54 and 56. There is insufficient antecedent basis for this limitation in the claim. The claims are drawn to a method for inhibiting HIV or SIV infection of cells. There is insufficient antecedent basis to support administering an antibody to a "subject" when the claims are drawn to a method of inhibiting infection of cells.

13. Claims 54-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "inhibiting" in claims 54 and 56 is a relative term which renders the claim indefinite. The term "inhibiting" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear what degree of inhibition needs to occur.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hoxie, US Patent 5,994,515, now US RE39,057 E (4 April 2006, benefit to 25 June 1996). Hoxie teaches antibodies directed against cellular coreceptors for human immunodeficiency virus, including CCR5 and methods of using the same.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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